

## Elimination of pethidine and bupivacaine in the newborn

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**SUMMARY** Pethidine or an epidural injection of bupivacaine are common forms of obstetric analgesia in Britain. Bupivacaine has been thought to have little effect on the fetus, but neuro-behavioural studies have cast doubt on this. We therefore investigated the elimination of these drugs by babies in similar population groups. Bupivacaine was largely eliminated in just over one day, while pethidine required between 2 and 6 days. This could account for the persisting depression in babies whose mothers had received pethidine.

At present in Britain the most commonly used analgesics in labour are pethidine or epidural bupivacaine. Pethidine is known to depress the respiration of the newborn baby (Schnider and Moya, 1964). This effect was least if the analgesic was given in a single dose within one hour of delivery. Bupivacaine, though known to cross the placenta (Belfrage *et al.*, 1975a), was thought to have little effect on the baby. Neurobehavioural scoring has given new information on the assessment of these drugs. Pethidine decreased the newborn response to behavioural tests as did lignocaine and mepivacaine (Brackbill *et al.*, 1974; Scanlon *et al.*, 1974). We have studied the elimination of pethidine and bupivacaine in the first few days of life.

### Method

There were 19 mothers in each group. All were aged between 20 and 35 years. The mean weight of the mothers given bupivacaine was 73.4 kg ( $\pm 12.1$  SD) and duration of labour averaged 6 hours 40 minutes. The mean weight of the group of mothers given pethidine was 72.9 kg ( $\pm 8.5$  SD) and average duration of labour was 6 hours 58 minutes. None had cardiovascular or respiratory disease. The purpose of the study was explained in detail to each woman and her consent obtained. The babies were all normal and of more than 36 weeks' gestation, mean birthweight being 3.4 kg ( $\pm 0.33$  SD). Analgesics were given as required. 16 mothers received a single dose of pethidine 150 mg intramuscularly and in 3 this was repeated once. Bupivacaine was administered epidurally in 0.25% concentration,

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\*We regretfully report the death of Miss Cooper on April 15. *Editors.*

usually in 10 ml doses, and the total amount necessary for patient comfort ranged from 25–185 mg with an average of 84 mg. After a pilot study it seemed inappropriate to take blood samples for each drug at the same time intervals. Therefore, in the pethidine group samples were taken at delivery from the mother and from cord blood, then at 2, 4, 8, 12, 24 hours and at 2, 3, 4, and 5 days from the baby. With the mothers receiving bupivacaine samples were taken at delivery, then at 2, 4, 8, 12, and 24 hours. Delivery samples were taken from the maternal antecubital vein and the umbilical vein. Samples were obtained from the babies by heel prick.

Pethidine was extracted by a method described by Beckett and Taylor (1967), and bupivacaine as described by Reynolds and Beckett (1968). After extraction from plasma the drugs were estimated by gas chromatography using a nitrogen detector.

### Results

In the first group were 12 patients who had a single dose of pethidine between 1 and 4 hours before delivery, and a second group of 4 where the injection-delivery interval was less than 1 hour. In the third group were 3 mothers who had two doses of pethidine within 8 hours of delivery.

The top part of Fig. 1 shows the changes with time of the pethidine levels where the injection-delivery time interval was 1–4 hours. Here most of the levels are 0.5  $\mu\text{g/ml}$  or less and the babies had largely eliminated the drug by 72 hours. The one baby with the persistently high levels had Apgar scores of 2 (1 minute) and 7 (5 minutes). Hypoxia depressing liver enzymes could account for this. The mother of this baby was herself sleepy for several days. The baby with the high postdelivery

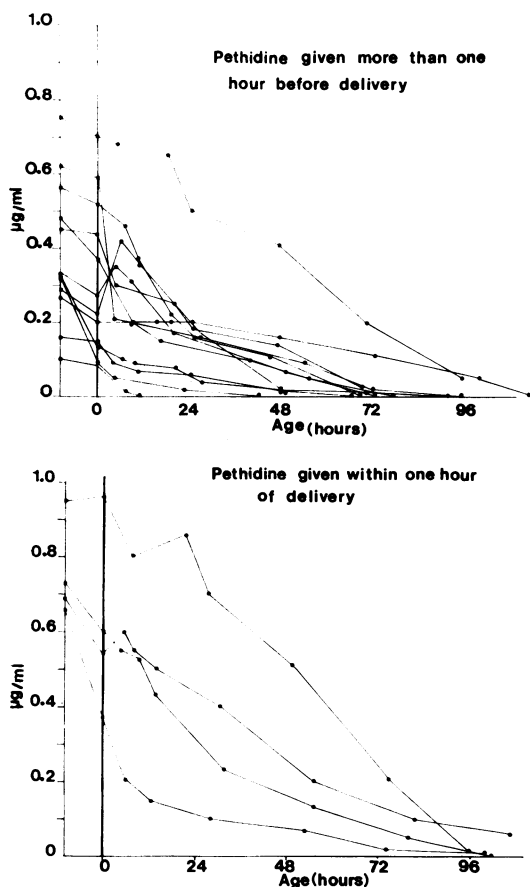


Fig. 1 Blood levels in babies whose mothers had a single dose of pethidine during labour. The points on the extreme left are the maternal levels.

peak had become hypoxic and his mother had had an intrapartum haemorrhage of 500 ml. The lower part of Fig. 1 shows the levels where the mothers had received pethidine within 1 hour of delivery. These levels began appreciably higher and remained so for at least 72 hours. In all of these mothers there was a significant relationship between the dose-delivery interval and the concentration in both maternal and cord blood ( $P < 0.001$ ).

Fig. 2 shows the data from the three mothers who had two doses of pethidine. Elimination was slow in their babies in the first 48 hours but the drug had largely disappeared by 96 hours. The cord-maternal ratio for the whole group was  $0.74 (\pm 0.35 \text{ SD})$  an indication that pethidine readily crosses the placenta. Total elimination seemed a reasonable end-point so we constructed a histogram

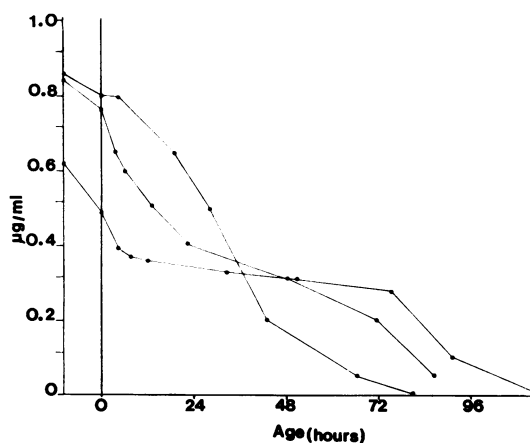


Fig. 2 Blood levels in babies whose mothers had two doses of pethidine during labour. The points on the extreme left are the maternal levels.

showing this (Fig. 3). 14 of the babies took 2 to 5 days to achieve this while 3 took even longer.

With bupivacaine the picture was very different. Again the levels are expressed as plasma concentrations in  $\mu\text{g/ml}$  but the time scale is 0-24 hours in 6-hour intervals. As can be seen in Fig. 4 the maternal levels go up to  $0.3 \mu\text{g/ml}$  but the cord-maternal ratio is  $0.59 (\pm 0.17 \text{ SD})$ , significantly less than for pethidine. As many of the patients had multiple doses of bupivacaine at variable intervals

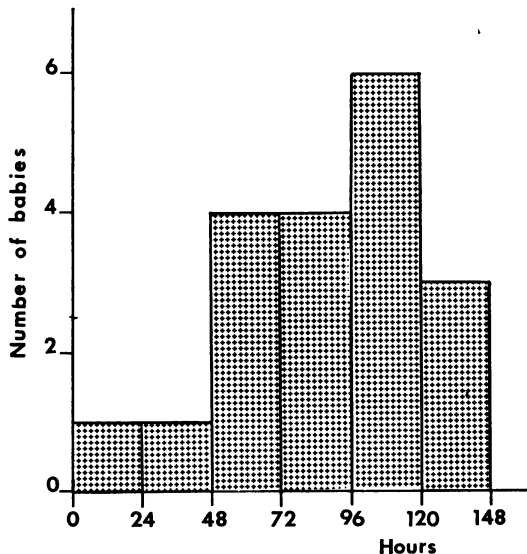


Fig. 3 The time taken for the elimination of pethidine from the blood of newborn babies is shown.

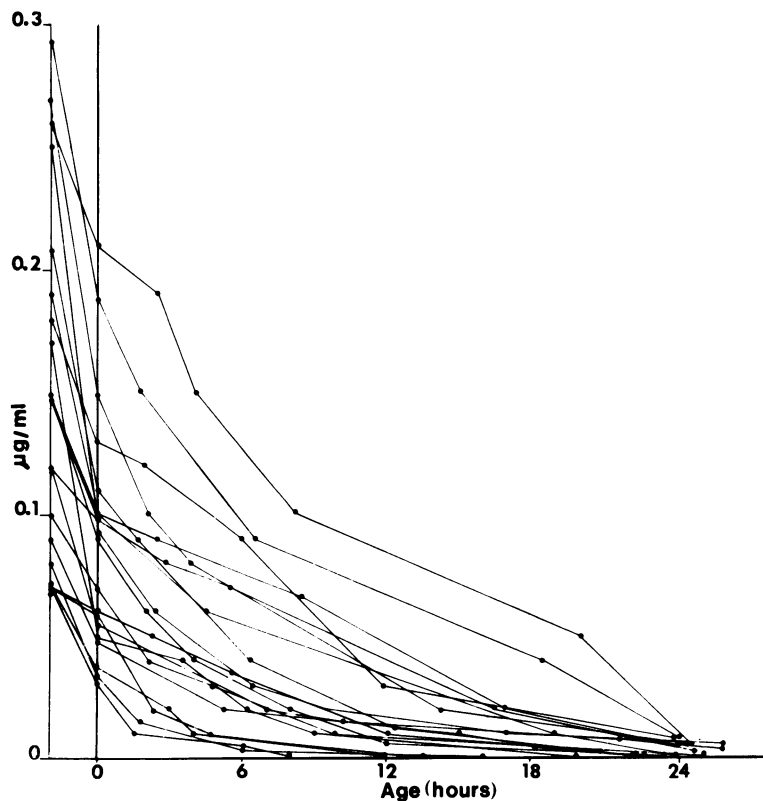


Fig. 4 Blood levels in babies whose mothers had an epidural injection with bupivacaine during labour. The points on the extreme left are the maternal levels.

it was not possible to prove a relationship between the dose-delivery time interval and blood levels. In individual cases some comment is possible. The patient with the highest level of bupivacaine had only 25 mg but this was given 48 minutes before delivery. This is the time of peak levels in the mother and possibly of peak transfer to the fetus (Magno *et al.*, 1976). 11 of the babies had eliminated bupivacaine within 24 hours whereas 2 had a level of 0.01  $\mu\text{g/ml}$  after that time. Another 6 had very low levels of 0.005  $\mu\text{g/ml}$  between 24 and 26 hours. The 2 babies who had appreciable levels after 24 hours were ones whose mothers had received relatively high doses of drug, namely 60 mg in 2 hours and 130 mg in 5½ hours. Fig. 5 illustrates the results of bupivacaine elimination.

#### Discussion

The blood level of a drug is not necessarily an index of effect but does indicate the rate of elimination of that drug. Bupivacaine and pethidine are absorbed readily and reach their peak blood levels within the first hour. Obviously during this time most of the

drug is presented to the placenta and the fetus. The higher protein binding of bupivacaine seemed to confer a safety factor to the fetus, in comparison to pethidine. High tissue affinity has been proven for etidocaine and probably exists for bupivacaine (Finster, 1976). Thus bupivacaine will go into the fetus and bind to the tissues, thereby increasing the transplacental concentration gradient. Therefore, much more bupivacaine crosses the placenta than was formerly thought. Even so, these drugs have to go back into the blood to be metabolized in the liver before excretion. □

The only comparable study is that of Belfrage *et al.* (1975b). Their neonatal bupivacaine levels appeared to be similar but the elimination was appreciably slower where 7 of 10 babies had levels above 0.01  $\mu\text{g/ml}$  at 20 hours. Their cord-maternal ratio was 0.27 ( $\pm 0.09$  SD). These differences could be due in part to the fact that they were using whole blood for their estimations whereas we used plasma. The venous-cord/maternal ratio is probably of limited value because it must be dependent on the tissue affinity of the drug and the concentration across the placenta, and therefore on the dose-

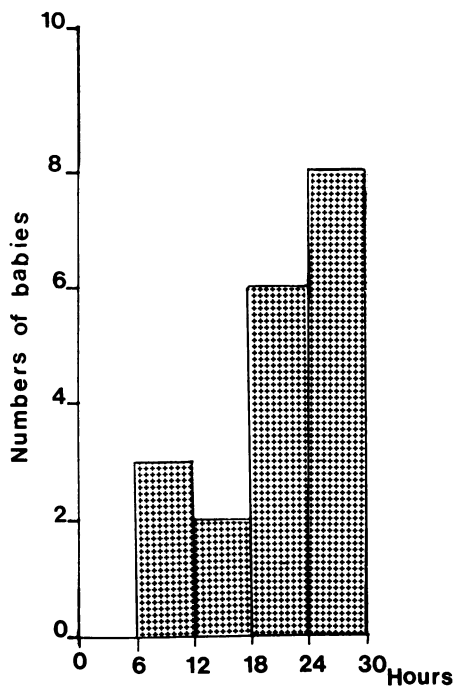


Fig. 5 The time taken for elimination of bupivacaine from the blood of newborn babies is shown.

delivery time interval. This is very variable in both series.

In this study our babies had virtually eliminated all the bupivacaine in the first day of life. In contrast those babies whose mothers had received pethidine took 3 to 6 days to achieve this. There was also in these latter babies a dose-effect relationship, but there was still considerable variation in the elimination rates. The babies whose mothers received pethidine within one hour of delivery had relatively high blood levels. In this instance where the drug is entering the body the blood level is probably a poor index of tissue content which may still be low. At this stage there may be little of the pethidine metabolized. Pethidine metabolites have been shown to cause respiratory depression (Stephen

and Cooper, 1977). These two factors may explain the paradoxical effect of minimal fetal depression when pethidine is given within one hour of delivery.

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